ET-1, promoted the pathophysiological phenotypes of HCM in the iPSC-derived cardiomyocytes.

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Endothelin receptor antagonists exacerbate autoimmune myocarditis in mice

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Background: Experimental autoimmune myocarditis (EAM) is a mouse model of inflammatory cardiomyopathy. The amount of endothelin (ET) increases according to the disease progression; however, the pathological role of ET in myocarditis has not been elucidated. Methods and results: EAM was induced by immunization of cardiac myosin peptide with complete Freund's adjuvant on days 0 and 7 in BALB/c mice. ET-A/-B dual receptor antagonist SB209670 was administered by continuous infusion from a subcutaneous pump for 3 weeks. An increase in heart-to-body weight ratio was observed in SB209670-treated mice compared with vehicle-treated mice. The heart pathology in SB209670-treated mice was remarkable for gross inflammatory infiltration, in contrast to the smaller inflammation in the hearts of vehicle-treated mice. We found that ET blockade decreased the number of Foxp3 + regulatory T cells and inhibited the production of immunoregulatory cytokine IL-10 in the heart. ET blockade also inhibited the expression of suppressor of cytokine signaling 3 (SOCS3) that plays a key role in the negative regulation of both Toll-like receptor (TLR)- and cytokine receptor-mediated signaling. EAM is a CD4 + T cell-mediated disease. CD4 + T cells isolated from SB209670-treated EAM mice produced less IL-10 and more inflammatory cytokines IFN-γ and IL-17 than those isolated from vehicle-treated mice. Conclusions: ET receptor antagonist exacerbated autoimmune myocarditis in mice. ET may play an important role in the regulation of inflammation in myocarditis.

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Imaging of the binding of ET-1 and of linear ET-1 in rat mesenteric resistance arteries

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In engineered cells, endothelin ETA- and ETB-receptors can heterodimerize. We tested whether this is possible in native tissue. Therefore, rat mesenteric resistance arteries were maintained in organ culture for 24 h to upregulate ETB-mediated contractions in addition to their normal ETA-mediated constrictions. Thereafter the vessels were cannulated and maintained at constant distending pressure and 37 °C under a two photon laser scanning microscope. They were then subsequently exposed to first 100 nM linear ET-1 (ETB-agonist) tagged with Oregon Green 488 (OG488) and then to 16 nM intact ET-1 (ETA/ETB-agonist) tagged with the rhodamine dye TAMRA. After incubation with the labeled ligands, the arterial smooth muscle cells in the tunica media were efficiently stained and became visible under the two photon microscope. Wrinkling of the autofluorescent internal and external elastic laminae accompanied agonist-induced constriction. TAMRA-ET-1 bound to all smooth muscle cells with a homogeneous cytoplasmic distribution whereas similar staining was observed for labeled linear ET-1 but only on some group of cells. Fluorescence lifetime measurements were employed to probe the interaction of the two receptor subtypes. Fluorescence lifetime of OG488, which acted as a donor, was reduced in the presence of TAMRA, from 2.8 ps to 2.3 ps, which indicates a fluorescence resonant energy transfer (FRET), a phenomenon which can take place only if the receptors are in close proximity (<10 nm). The methodology that is introduced by these preliminary observations may be useful to asses ET-receptor heterodimerization in biopsies from relevant experimental animal models and human patients.

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Sympathetic endothelin A receptors contribute to the development of heart failure

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In preclinical heart failure (HF) models, endothelin receptor A (ETA) antagonists (ETAi) attenuated the disease progression. However, clinical HF trials failed to demonstrate beneficial effects on cardiac function and prognosis. We hypothesized that established HF drugs such as adrenergic receptor blockers interfere with the mechanism of action of ETAi. Here we report, that mice lacking ETA selectively in sympathetic neurons (SN-KO) showed less adverse structural remodeling and cardiac dysfunction in response to pathological pressure overload induced by transverse aortic constriction (TAC). In contrast, mice lacking ETA selectively in cardiomyocytes (CM-KO) were not protected against HF. TAC led to a disturbed sympathetic nerve function as measured by cardiac norepinephrine (NE) tissue levels and [124I]-MIBG PET, which was prevented in SN-KO. In co-cultures of cardiomyocytes (CMs) and sympathetic neurons (SNs), endothelin-1 (ET1) led to a massive NE release and exaggerated CM hypertrophy as compared to CM mono-cultures. ETA-deficient CMs gained a hypertrophic response through wild type SNs but ETA-deficient SNs failed to mediate exaggerated CM